Benefit of Glycoprotein IIb/IIIa Inhibition in Patients With Acute Coronary Syndromes and Troponin T–Positive Status

The PARAGON-B Troponin T Substudy

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Background—Troponin T (TnT) is valuable for short- and long-term risk stratification of patients with acute coronary syndromes (ACS). It also may predict which ACS patients will benefit from glycoprotein (GP) IIb/IIIa blockade.

Methods and Results—We prospectively studied 1160 patients with non–ST-segment elevation ACS randomized in PARAGON-B to receive lamifiban, an intravenous GP IIb/IIIa antagonist, or placebo. TnT levels were obtained before study treatment began and 24 to 72 hours later; assays were performed by a blinded core laboratory. At baseline, 40.2% of patients were TnT-positive (≥0.1 ng/mL); these patients were older and more often male or smokers. Patients positive at baseline had a significantly higher rate of the primary end point (composite of death, myocardial (re)infarction, or severe recurrent ischemia at 30 days; odds ratio, 1.5; 95% CI, 1.1 to 2.1) than those who were TnT-negative. Lamifiban was associated with significant reduction in the primary end point (from 19.4% to 11.0%, \( P = 0.01 \)) among TnT-positive patients but not among TnT-negative patients (11.2% for placebo versus 10.8% for lamifiban, \( P = 0.86 \); \( P = 0.08 \) for test of interaction between TnT status and treatment assignment). This pattern held for the end points of death alone and death or myocardial (re)infarction at 30 days. Peak TnT level at 48 hours did not differ with lamifiban treatment.

Conclusions—TnT predicts poor short-term outcomes in non–ST-segment elevation ACS. Treatment benefit with lamifiban is limited almost exclusively to TnT-positive patients, reducing 30-day adverse outcomes to a rate nearly identical to that of negative patients. (Circulation. 2001;103:2891-2896.)

Key Words: coronary disease ♦ troponins ♦ prognosis ♦ platelets ♦ inhibitors

Patients with non–ST-segment elevation acute coronary syndromes (ACS) who are troponin T (TnT)–positive at admission are at higher risk for death and myocardial (re)infarction (MI), and angiographic studies show that they also are more likely to have an “active” plaque with thrombus in the culprit vessel. Retrospective studies suggest that such patients may show an enhanced treatment effect with platelet glycoprotein (GP) IIb/IIIa inhibitors or low-molecular-weight heparin. GP IIb/IIIa inhibition may also modulate the magnitude of troponin release.

In the c7E3 Fab AntiPlatelet Therapy in Unstable REfractory angina (CAPTURE) study, 1265 patients with refractory unstable angina scheduled for angioplasty were randomized to abciximab or placebo after a mean of 5 days of hospitalization. There was 60% less death or nonfatal MI at 6 months with abciximab treatment among patients who were TnT-positive at randomization, whereas patients who were TnT-negative showed no treatment effect. In a retrospective analysis of 2222 patients enrolled in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study, troponin status at a mean of 8.4 hours after symptom onset was determined. The rate of death or MI among patients given tirofiban and aspirin who were troponin I (TnI)–positive was 4.3%, compared with 13% for those receiving heparin and aspirin. Patients who were TnI-negative showed no significant treatment effect.

The Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON)-B study was a double-blind, randomized, placebo-controlled trial designed to assess the effect of lamifiban, a short-acting, nonpeptide, small-molecule GP IIb/IIIa antagonist, dosed according to renal function to achieve target plasma concentrations, on 30-day outcomes. We conducted a prospective substudy of PARAGON-B to assess any interaction between treatment effects and baseline TnT status among patients receiving aspirin and heparin for...
non–ST-segment elevation ACS. Our primary hypothesis was that treatment effect would be greater among patients who were TnT-positive at baseline. We also explored the relation between treatment effect and peak TnT level at 24 to 72 hours.

Methods
The TnT substudy was designed simultaneously with the overall PARAGON-B project. A total of 1160 patients from 105 hospitals in 14 countries participated. The institutional review board at each site approved the substudy protocol.

Patient Population
The PARAGON-B protocol has been described in detail. In brief, patients >21 years of age with non–ST-segment elevation ACS who presented within 12 hours of symptom onset and who had symptoms lasting ≥10 minutes were eligible. All patients were required to have evidence of cardiac ischemia, either ECG changes or elevated creatine kinase-MB or TnT or TnI by local laboratory standards. Excluded were patients with increased bleeding risk, planned or recent thrombolysis, use of other GP IIb/IIIa therapy, recent major surgery, estimated creatinine clearance <30 mL/min, or contraindication to aspirin or heparin.

Eligible patients were randomized equally to either lamifiban or placebo in a double-blind fashion. Patients assigned to lamifiban received a bolus of 500 μg, followed by an infusion adjusted for renal function targeting a steady-state plasma lamifiban concentration of 18 to 42 ng/mL. Study drug was continued for up to 72 hours, and all patients received standard-dose aspirin and intravenous heparin (unfractionated or low molecular weight). Medical stabilization was recommended for ≥24 hours before any percutaneous coronary intervention (PCI).

TnT Determinations
For all substudy patients, 10 mL of blood was collected for TnT measurement at enrollment; in 346 patients at selected sites, another sample was obtained at 24 to 72 hours after randomization but before study drug was terminated. All samples were collected in tubes containing either citrate (to yield plasma) or no anticoagulant (allowed to clot for 30 minutes, to yield serum). Specimens were centrifuged for 10 minutes at 1500 g, and the resulting plasma or serum was frozen immediately and maintained locally at −20°C or lower. Samples were shipped in batches on dry ice to the core laboratory (University of Maryland).

All TnT measurements were performed with the third-generation TnT STAT electrochemiluminescence immunoassay on the Elecsys 2010 system (Roche Diagnostics Corp). The minimum detectable concentration of this system is 0.01 ng/mL, and typical precision is 6.2% at concentrations of both 0.15 and 6 ng/mL. The prespecified positive threshold used in this study was a TnT level ≥0.1 ng/mL, based on studies that have identified this level as optimal for risk stratification for 30-day mortality. Personnel performing the TnT analyses were blinded to both treatment assignment and clinical outcomes.

Data Collection and Statistical Analysis
Baseline demographic and clinical information was derived from the main PARAGON-B database. The study’s primary end point was a 30-day composite of death, MI, or severe recurrent ischemia requiring urgent intervention. The main secondary end point was a composite of death or MI. End points were defined and adjudicated by a central committee as in the main trial.

Descriptive statistics (medians with interquartile ranges for continuous variables and percentages for discrete variables) were generated for baseline characteristics and outcomes. Logistic regression was used to assess the relation of baseline TnT status to clinical outcomes and any interaction between baseline TnT status and other covariates.
interaction term.

0.320). The adjudicated rate of MI was slightly higher in patients in the larger study (20% versus 3.25% among patients in the larger study overall (OR, 0.96; P=0.006) and the composite of death or MI (OR, 2.04; P=0.003), but there was no difference with lamifiban versus placebo treatment in the substudy overall (OR, 0.92; P=0.92, respectively). Although formal tests for interaction were not significant, there were trends for interactions between treatment effect and troponin status for the primary end point.

### Results

A baseline TnT sample was obtained for 1160 substudy patients; 346 patients had a second, 24- to 72-hour, sample. There were no major differences in baseline characteristics between patients in the substudy (22% of the total PARAGON-B population) and those who were in the larger study (Table 1). There were more patients from Eastern Europe in the substudy overall (OR, 0.96; P=0.006) and those in the larger study (12.76% versus 11.98%, P=0.480). The primary composite end-point rates did not differ significantly between patients in the substudy and those in the larger study (12.76% versus 11.98%, P=0.480).

Overall, 466 patients (40.2%) tested TnT-positive and 694 (59.8%) were TnT-negative at enrollment. The median TnT level in positive patients was 0.43 ng/mL (interquartile range, 0.21 to 0.93 ng/mL), and the corresponding value for negative patients was 0 ng/mL (0 to 0.03 ng/mL). TnT-positive patients were older, were more likely to be men and current smokers, and had had chest pain longer before enrollment (Table 1). The most common presenting ECG finding in positive patients was ST-segment depression (51.7%), whereas T-wave inversion was most common in negative patients (50.3%). Although unusual, normal ECGs were more frequent among TnT-negative patients, as was transient ST-segment elevation among TnT-positive patients. No other major differences in baseline characteristics were observed.

Clinical end points by TnT status are shown in Table 2. TnT-positive patients had significantly higher rates of the primary composite end point (P=0.025), the composite of death or MI (P=0.007), mortality alone (P=0.007), and MI alone (P=0.044) than the TnT-negative patients.

The treatment effect of lamifiban by TnT status is shown in Table 3. Three patients, 2 TnT-positive and 1 TnT-negative, for whom treatment information was unavailable were eliminated from these analyses. In the TnT-positive group, significant treatment effects of lamifiban were noted for both the primary end point (P=0.013) and the composite of death or MI (P=0.018). In an exploratory analysis, results were similar among 331 medically treated TnT-positive patients. For both the primary end point and the death or MI composite, the event rate among lamifiban-treated patients was 10.9%, compared with 16.9% in the placebo group; OR 0.60 (0.32, 1.1). No such effect was noted in the TnT-negative patients (P=0.86 and P=0.75, respectively). Most of the treatment effect reflected reductions in mortality (39%) and MI (46%). The treatment effect of lamifiban on mortality in TnT-positive patients, however, did not reach statistical significance (P=0.29) with this sample size. At 6 months, the composite of death or MI did not differ significantly in TnT-positive patients treated with lamifiban versus placebo (P=0.21).

The interaction between treatment and TnT status is shown in Figure 1. Patients who were TnT-positive had significantly higher rates of the primary end point (OR, 1.91; P=0.006) and the composite of death or MI (OR, 2.04; P=0.003), but there was no difference with lamifiban versus placebo treatment in the substudy overall (OR, 0.92; P=0.92, respectively). Although formal tests for interaction were not significant, there were trends for interactions between treatment effect and troponin status for the primary end point.

### Table 2. Clinical Outcomes at 30 Days by Baseline TnT Status

<table>
<thead>
<tr>
<th></th>
<th>TnT-Positive (n=468)</th>
<th>TnT-Negative (n=694)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point, %*</td>
<td>15.5</td>
<td>11.0</td>
</tr>
<tr>
<td>Death or (re)infarction, %</td>
<td>15.2</td>
<td>9.9</td>
</tr>
<tr>
<td>Death, %</td>
<td>4.3</td>
<td>1.6</td>
</tr>
<tr>
<td>(Re)Infarction, %</td>
<td>13.3</td>
<td>9.5</td>
</tr>
<tr>
<td>Severe recurrent ischemia, %</td>
<td>0.4</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*Death, (re)infarction, or severe recurrent ischemia.

### Table 3. Clinical Outcomes at 30 Days by Baseline TnT Status and Treatment Assignment

<table>
<thead>
<tr>
<th></th>
<th>Lamifiban (n=227)</th>
<th>Placebo (n=237)</th>
<th>Lamifiban (n=344)</th>
<th>Placebo (n=349)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point, %*</td>
<td>11.0</td>
<td>19.4</td>
<td>10.8</td>
<td>11.2</td>
</tr>
<tr>
<td>Death or (re)infarction, %</td>
<td>11.0</td>
<td>19.0</td>
<td>9.6</td>
<td>10.3</td>
</tr>
<tr>
<td>Death, %</td>
<td>3.1</td>
<td>5.1</td>
<td>1.2</td>
<td>2.0</td>
</tr>
<tr>
<td>(Re)Infarction, %</td>
<td>9.3</td>
<td>17.3</td>
<td>9.3</td>
<td>9.7</td>
</tr>
<tr>
<td>Severe recurrent ischemia, %</td>
<td>0.4</td>
<td>0.4</td>
<td>1.5</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*Death, (re)infarction, or severe recurrent ischemia.
end point (OR, 0.54; \( P = 0.085 \)) and the death or MI composite (OR, 0.57; \( P = 0.132 \)).

The effects of lamifiban among TnT-positive and -negative patients on other selected clinical outcomes and bleeding complications are shown in Table 4. Overall, TnT-positive patients had higher rates of PCI and bypass surgery than did TnT-negative patients. Major bleeding did not differ by troponin status. There were no significant differences in these events by treatment in either the TnT-positive or -negative group, but the rates of PCI and readmission were somewhat lower among lamifiban- versus placebo-treated TnT-positive patients. Although the absolute numbers were low, the difference in stroke rates between lamifiban- and placebo-treated TnT-positive patients was not significant. There was no difference in the effect of lamifiban versus placebo on bleeding rates by TnT status.

Follow-up samples were available in 346 patients at a median 45.3 (27.3 to 49.3) hours after randomization. Among patients who were TnT-positive at baseline, TnT levels increased slightly at the second sample, from \( 0.50 \) (0.23 to 1.38) to \( 0.78 \) (0.23 to 1.46) ng/mL; \( P = 0.197 \). Overall, the median TnT level at the second sample did not differ significantly by treatment (lamifiban versus placebo: \( 0.14 \) (0 to 0.76) ng/mL for lamifiban versus \( 0.10 \) (0 to 0.70) for placebo; \( P = 0.76 \)). Results were similar when patients who underwent revascularization between the first and second samples \( (n = 38) \) were excluded (data not shown).

**Discussion**

This prospective study supports the proposition that a GP IIb/IIIa antagonist can neutralize the heightened risk of TnT-positive patients with non–ST-segment elevation ACS. As evidenced by the borderline-significant interaction term between troponin status and treatment, which held true for both the primary end point and the composite of death or MI, this study strongly suggests that the treatment effect of lamifiban in patients with ACS is focused among those who are TnT-positive.

Previous studies carried out in North America or in single European countries have noted greater mortality among troponin-positive patients.\(^1,2,5,10\) This study extends the observation of the powerful ability of TnT elevation to predict an increased risk of mortality or nonfatal MI to a broad range of healthcare settings and practice patterns around the world.

This study is now the third published to suggest that the treatment effect of GP IIb/IIIa antagonists is amplified in patients with a positive troponin level. As shown in Table 5, however, our study differs in several important ways from previous studies. First, the 2 previous studies\(^5,6\) were retrospective; the substudies were not initiated until after the main trials were completed. Second, the study methods and patient populations in these studies varied widely and were limited in their ability to generalize to practice settings. In the CAPTURE trial of abciximab, only patients who had failed standard medical therapy and were suitable for PCI after angiography were enrolled.\(^11\) The PRISM trial tested only tirofiban, without concomitant heparin, for 48 hours of medical stabilization, without continued therapy during PCI.\(^12\) Nevertheless, the findings from our study with lamifiban are similar to those described by Heeschen and colleagues\(^6\) with tirofiban. Although it was not a statistically proper subgroup comparison in our study, like the PRISM investigators, we found that our results are similar in medically and interventionaly treated patients.

Figure 2 displays a systematic overview of the relationship of troponin status and treatment effect on the end point of

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**TABLE 4. Bleeding and Readmissions at 30 Days by Baseline TnT Status and Treatment Assignment**

<table>
<thead>
<tr>
<th></th>
<th>TnT-Positive</th>
<th></th>
<th>TnT-Negative</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lamifiban (n=227)</td>
<td>Placebo (n=237)</td>
<td>Lamifiban (n=344)</td>
<td>Placebo (n=349)</td>
</tr>
<tr>
<td>PCI, %</td>
<td>27.3</td>
<td>30.0</td>
<td>22.4</td>
<td>23.2</td>
</tr>
<tr>
<td>Bypass surgery, %</td>
<td>16.7</td>
<td>15.6</td>
<td>11.9</td>
<td>9.7</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>1.8</td>
<td>0.4</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Intracranial hemorrhage, %</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blood transfusion, %</td>
<td>11.0</td>
<td>10.1</td>
<td>8.7</td>
<td>6.9</td>
</tr>
<tr>
<td>Major bleeding, %</td>
<td>0.9</td>
<td>0.4</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Readmission (any cause), %</td>
<td>12.8</td>
<td>14.3</td>
<td>13.7</td>
<td>11.7</td>
</tr>
</tbody>
</table>
TABLE 5. Treatment Effect by TnT Status in Various Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study Design</th>
<th>Population</th>
<th>Death or MI, TnT+, %</th>
<th>Relative Reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRISM</td>
<td>2222</td>
<td>Retrospective</td>
<td>ACS</td>
<td>Treatment 3.5</td>
<td>13.7</td>
</tr>
<tr>
<td>CAPTURE</td>
<td>1265</td>
<td>Retrospective</td>
<td>ACS + PCI</td>
<td>Treatment 5.8</td>
<td>19.6</td>
</tr>
<tr>
<td>PARAGON-B</td>
<td>1160</td>
<td>Prospective</td>
<td>ACS</td>
<td>Treatment 11.0</td>
<td>19.0</td>
</tr>
<tr>
<td>PRISM-PLUS</td>
<td>110</td>
<td>Retrospective</td>
<td>ACS</td>
<td>Treatment 3.6</td>
<td>20.6</td>
</tr>
<tr>
<td>GUSTO IV</td>
<td>7707</td>
<td>Prospective</td>
<td>ACS</td>
<td>Treatment 10.5</td>
<td>10.7</td>
</tr>
</tbody>
</table>

†The GUSTO IV ACS Investigators; presented at the XCI Congress of the European Society of Cardiology.

figure 2.png

Figure 2. Odds ratios with 95% CI for death or MI among troponin-negative and -positive patients and for interaction of troponin status with treatment effect for PRISM, CAPTURE, PARAGON-B, and combined trials. Values to left of 1.0 indicate a benefit of GP IIb/IIIa inhibition.

dehart or MI in 3 published studies. Odds ratios from the 3 studies were combined by use of an empirical Bayes random-effects model. Consistently in all studies, there was no evidence of benefit with a GP IIb/IIIa antagonist in troponin-negative patients (combined OR, 1.06; 95% CI, 0.78 to 1.43). Among troponin-positive patients, however, each study showed a significant treatment effect (combined OR, 0.34; 95% CI, 0.19 to 0.58). As noted, because of our limited sample size, we could not show a statistically significant interaction of troponin status with treatment. Nonetheless, consistent with both PRISM and CAPTURE, the point estimate supports such an interaction, and for the 3 studies, the combined odds ratio for treatment effect by troponin is highly significant (OR, 0.33; 95% CI, 0.19 to 0.57). The consistency of these 3 investigations suggests the particular benefit of GP IIb/IIIa receptor antagonists in troponin-positive patients across a spectrum of treatment indications and use patterns.

The overall results of the PARAGON-B study revealed a nonsignificant effect of lamifiban across a spectrum of patients with non–ST-segment elevation ACS. Our substudy suggests, however, that had enrollment in PARAGON-B been restricted to TnT-positive patients, the overall results might have been influenced in favor of treatment with lamifiban. The mechanism for the differential treatment effect of GP IIb/IIIa antagonists or low-molecular-weight heparins among troponin-positive versus -negative ACS patients most likely reflects their ability to prevent or minimize microvascular embolization or obstruction. Patients with positive troponins have been shown to have more extensive coronary disease, more complex lesions, and more often thrombus at the site of an active lesion. In the CAPTURE study, a comparison of angiography before and after administration of study drug showed a greater likelihood of thrombus resolution and greater improvement in Thrombolysis In Myocardial Infarction (TIMI) flow grade among patients receiving abciximab, supporting such a mechanism for improved outcomes in TnT-positive patients receiving GP IIb/IIIa antagonists. Thus, an elevated troponin level might serve as a marker for the optimal use of these agents in clinical practice in patients with ACS. Whether a similar effect of GP IIb/IIIa inhibition might occur in cohorts identified by other markers of increased risk, such as elevated creatine kinase-MB or profound ST-segment depression, remains to be investigated.

The treatment benefit with lamifiban among TnT-positive patients did not appear to be undermined by increased bleeding. The rates of intracranial hemorrhage, major bleeding, and blood transfusions were similar between this group and both the lower-risk, TnT-negative patients and the overall study cohort. The previously described studies have not reported similar data for tirofiban or abciximab.

There appeared to be no effect of lamifiban on the magnitude of TnT values in later samples, obtained a median of 45 hours after the infusion was started. One small study of 105 patients showed lower peak and mean TnI levels on serial sampling over 24 hours in patients randomized to tirofiban plus heparin in the PRISM-PLUS trial. Although this could reflect less myocardial damage with GP IIb/IIIa inhibition, no studies have identified the optimal timing of troponin sampling to “size” MIs, and there may be differences between troponins T and I. Previous investigators have described a bimodal distribution of peak TnT levels, but not TnI levels, after MI. The first TnT peak occurs in the first 12 to 24 hours after symptom onset, whereas the second, more sustained peak occurs at 72 to 96 hours. With only a single second sample obtained at 24 to 72 hours, we could have missed the true peaks in a substantial proportion of patients.

There are some limitations to the present study. The rate of troponin positivity (40%) in this study was slightly higher than in other observations (30%), suggesting that higher-risk patients were recruited. The PRISM trial showed a lower rate of TnT-positivity (29%); yet the results among those TnT-
positive patients are similar to those of the present study. Nevertheless, one should be cautious in extending these observations to lower-risk cohorts of TnT-positive patients.

The results of our study and 2 previous studies are in conflict with the preliminary results of the Global Use of Strategies To open Occluded arteries-IV Acute Coronary Syndromes (GUSTO IV ACS) study presented at the XXII Congress of the European Society of Cardiology, although consistent with a small subgroup of PRISM-PLUS (J.L. Januzzi, personal communication) (Table 5). GUSTO IV ACS showed no benefit of abciximab for treatment of ACS in a population in which local laboratory troponin-positive status was used in part to define study eligibility. The unexpected results of GUSTO IV ACS may be explained by one or a combination of several factors: (1) the lack of PCI in GUSTO IV (<2% compared with 100% in CAPTURE), (2) slightly different entry criteria from other ACS trials, (3) dosing strategies of abciximab that are probably suboptimal in ACS, or (4) differences between local and core laboratory troponin measurements. The evidence from 4 of 5 studies, however, supports an enhanced effect of GP IIb/IIIa antagonists in patients who are troponin-positive at baseline.

In summary, our results further confirm that TnT status is a powerful tool for risk stratification. In addition, although the rate of death or MI at 30 days remained nearly 10% even among TnT-negative patients, the use of a GP IIb/IIIa receptor antagonist such as lamifiban appeared to neutralize the heightened risk for adverse cardiac events among TnT-positive patients, resulting in a level similar to that of TnT-negative patients. Given the diversity of the non–ST-segment elevation ACS population and inherent limitations in clinical and ECG risk stratification, our results, in conjunction with similar findings in previous studies, suggest that positive TnT status is an important additional consideration in the decision to use a GP IIb/IIIa receptor antagonist.

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References

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